

CLAIMS

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- 3
- 4 1. A method of treating rhinosinusitis or alleviating the symptoms of rhinosinusitis,
- 5 comprising
- 6 administering an agent that permits the release of proteins from the endoplasmic
- 7 reticulum.
- 8
- 9 2. The method of claim 1, wherein the agent is delivered intranasally.
- 10
- 11 3. The method of claim 1, further comprising the step of:
- 12 providing an individual suffering from rhinosinusitis.
- 13
- 14 4. The method of claim 3, wherein the providing step comprises providing an individual
- 15 suffering from chronic rhinosinusitis.
- 16
- 17 5. The method of claim 3, wherein the individual carries a mutation in at least one copy of a
- 18 gene encoding a cystic fibrosis transmembrane conductance regulator.
- 19
- 20 6. The method of claim 3, wherein the gene is the *CFTR* gene.
- 21
- 22 7. The method of claim 3, wherein the individual carries a mutation in one copy of the gene.
- 23
- 24 8. The method of claim 3, wherein the individual carries a mutation in both copies of the
- 25 gene.
- 26
- 27 9. The method of claim 7 or claim 8, wherein the mutation is a  $\Delta F508$  mutation.
- 28
- 29 10. The method of claim 9, wherein the individual carries an M470V variant of the *CFTR*
- 30 gene.
- 31

1 11. A method of treating hemochromatosis or alleviating the symptoms of hemochromatosis,  
2 comprising

3 administering an agent that permits the release of proteins from the endoplasmic  
4 reticulum.

5  
6 12. The method of claim 11, further comprising the step of:  
7 providing an individual suffering from hemochromatosis.

8  
9 13. The method of claim 11, wherein the providing step comprises providing an individual  
10 having a mutation in at least one copy of a gene encoding an HFE protein.

11  
12 14. The method of claim 12, wherein the individual carries a mutation in one copy of the  
13 gene.

14  
15 15. The method of claim 12, wherein the individual carries a mutation in both copies of the  
16 gene.

17  
18 16. A method of treating Gitelman's syndrome or alleviating the symptoms of Gitelman's  
19 syndrome, comprising

20 administering an agent that permits the release of proteins from the endoplasmic  
21 reticulum.

22  
23 17. The method of claim 16, further comprising the step of:  
24 providing an individual suffering from Gitelman's syndrome.

25  
26 18. The method of claim 17, wherein the individual carries a mutation in at least one copy of  
27 a gene encoding a thiazide sensitive Na-Cl cotransporter.

28  
29 19. The method of claim 18, wherein the gene is the *NCC* gene.

30  
31 20. The method of claim 19, wherein the mutation is a G738R mutation.

1  
2 21. The method of claim 18, wherein the individual carries a mutation in one copy of the  
3 gene.

4  
5 22. The method of claim 18, wherein the individual carries a mutation in both copies of the  
6 gene.

7  
8 23. A method of treating cystinuria or alleviating the symptoms of cystinuria, comprising  
9 administering an agent that permits the release of proteins from the endoplasmic reticulum.

10  
11 24. The method of claim 23, further comprising the step of:  
12 providing an individual suffering from cystinuria.

13  
14 25. The method of claim 24, wherein the providing step comprises providing an individual  
15 suffering from type I cystinuria.

16  
17 26. The method of claim 24, wherein the individual carries a mutation in at least one copy of  
18 a gene encoding a subunit of an rBAT protein.

19  
20 27. The method of claim 26, wherein the individual carries a mutation in one copy of the  
21 gene.

22  
23 28. The method of claim 26, wherein the individual carries a mutation in both copies of the  
24 gene.

25  
26 29. The method of any of claims 3, 12, 17, or 24, wherein the agent is a calcium pump  
27 inhibitor.

28  
29 30. The method of any of claims 3, 12, 17, or 24, wherein the agent decreases or inhibits the  
30 activity of UDP glucose:glycoprotein glycosyl transferase.  
31



41. The method of any of claims 3, 12, 17, or 24, wherein the agent is an oligonucleotide which is antisense to a protein selected from the group consisting of UDP glucose:glycoprotein glycosyl transferase, calnexin and  $\text{Ca}^{++}$  ATPase.

42. A method of treating any disease or clinical condition, comprising administering an agent that permits the release of proteins from the endoplasmic reticulum, wherein the agent increases or activates ryanodine receptor activity.

43. The method of claim 42, wherein the disease is selected from the list consisting of: Cystic Fibrosis, Chronic Obstructive Pulmonary Disease, Paroxysmal Nocturnal Hemoglobinuria, Familial Hypercholesterolemia, Tay-Sachs Disease, viral diseases, neoplastic diseases, Hereditary Myeloperoxidase Deficiency, Congenital Insulin Resistance, Rhinosinusitis, Nephrogenic Diabetes Insipidus, Hemochromatosis, Gitelman's Syndrome, and Cystinuria.

44. A method of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell comprising the step of administering an agent that decreases or inhibits the functional activity of UDP glucose:glycoprotein glycosyl transferase.

45. A method of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell comprising the step of administering an agent that decreases or inhibits activity of the endoplasmic reticulum  $\text{Ca}^{++}$  ATPase.

46. A method of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell comprising the step of administering an agent that lowers the concentration of  $\text{Ca}^{++}$  in the endoplasmic reticulum.

47. A method of releasing a mis-assembled or mis-folded glycoprotein from the endoplasmic reticulum of a cell comprising the step of administering an agent that decreases or inhibits calnexin functional activity.

1 48. A method of increasing the permeability of the apical surfaces of airway epithelial cells to  
2 a chloride ion comprising the step of administering an agent that decreases or inhibits the  
3 intracellular retention of mis-assembled or mis-folded glycoproteins.  
4

5 49. A method of increasing the permeability of the apical surfaces of airway epithelial cells to  
6 a chloride ion comprising the step of administering an agent that decreases or inhibits the  
7 activity of UDP glucose:glycoprotein glycosyl transferase.  
8

9 50. A method of increasing the permeability of the apical surfaces of airway epithelial cells to  
10 a chloride ion comprising the step of administering an agent that decreases or inhibits activity  
11 of the endoplasmic reticulum  $\text{Ca}^{++}$  ATPase.  
12

13 51. A method of increasing the permeability of the apical surfaces of airway epithelial cells to  
14 a chloride ion comprising the step of administering an agent that lowers the concentration of  
15  $\text{Ca}^{++}$  in the endoplasmic reticulum.  
16

17 52. A method of increasing the permeability of the apical surfaces of airway epithelial cells to  
18 a chloride ion comprising the step of administering an agent that decreases or inhibits  
19 calnexin functional activity.  
20

21 53. A method of screening candidate compounds to identify an agent that inhibits  
22 endoplasmic reticulum-associated retention or degradation of a mis-assembled or mis-folded  
23 glycoprotein, wherein the method comprises the steps of:

- 24 a). treating a cell exhibiting intracellular retention of a mis-assembled or mis-  
25 folded glycoprotein in the endoplasmic reticulum with the candidate compound; and  
26 b). determining whether the mis-assembled or mis-folded glycoprotein is released  
27 from the endoplasmic reticulum, thereby identifying the candidate compound as an agent that  
28 causes the release of a malformed mis-folded glycoprotein from the endoplasmic reticulum.  
29

1 54. A method of screening candidate compounds to identify an agent that inhibits the  
2 functional activity of UDP glucose:glycoprotein glycosyl transferase, wherein the method  
3 comprises the steps of:

- 4 a). treating a cell exhibiting intracellular retention of a mis-assembled or mis-  
5 folded glycoprotein in the endoplasmic reticulum with the candidate compound; and  
6 b). determining whether the mis-assembled or mis-folded glycoprotein is released  
7 from the endoplasmic reticulum, thereby identifying the candidate compound as an agent that  
8 causes the release of a mis-assembled or mis-folded glycoprotein from the endoplasmic  
9 reticulum.

10  
11 55. A composition which comprises two or more agents selected from the group consisting of  
12 an agent that decreases or inhibits the activity of UDP glucose:glycoprotein glycosyl  
13 transferase, an agent that decreases or inhibits activity of the endoplasmic reticulum  $\text{Ca}^{++}$   
14 ATPase, an agent that stimulates or increases  $\text{IP}_3$  receptor activity, and an agent that decreases  
15 or inhibits calnexin functional activity.

16  
17 56. A composition comprising an aerosol formulation of thapsigargin, DBHQ or  
18 cyclopiazonic acid.